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10/523,999	02/09/2005	Maharaj K Sahib	WH-1	2848

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
12/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,999	SAHIB ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *130-133,135-137 and 140-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *130-133,135-137 and 140-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 130-133, 135-137 and 140-142 are pending. Claims 1-129, 134, 138 and 139 are cancelled; all objections and rejections of these claims are now moot.

Election/Restrictions

2. Applicant's traversal in the reply filed on 10/16/2008 of the election of the species isopropanol made by telephone on 06/02/2008 is acknowledged. The traversal is on the ground(s) that the compounds possess a common property of miscibility. This is not found persuasive because although the compounds share this common property, there is no evidence on record that they are obvious variants of each other. As a result, a prior art search of the species isopropanol would not necessarily yield documents pertaining to all of the other claimed species. The requirement is still deemed proper and is therefore made FINAL.

3. A prior art rejection is made over the elected species as well as over the additional species ethanol, methanol, and dioxin. As a result the search has not been extended to additional species in accordance with MPEP § 803.02.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 130, 131, 135-137, 141 and 142 are rejected under 35 U.S.C. 102(e) as being anticipated by Annibali (US Patent No. 7,091,032). Annibali teaches a process for the recovery of recombinant insulin including treating a culture medium comprising cells for expressing insulin with a water miscible solvent and isolating the insulin from the mixture (col. 25, lines 1-50). With respect to the limitation "treating an expression broth/culture medium containing the expressing cells with a one or more water miscible organic solvents to give a mixture", Annibali teaches that the purpose of the miscible solvent addition is to induce insulin expression. The process of adding methanol in Annibali occurs over a time period (col. 25, ln. 17-26):

> Once the growing phase of the biomass was completed, the cells were kept without feeding for half an hour and the production phase begun. During said phase pH was regulated from 3.5 to 5.5, and 100% methanol was added plus 12 ml/l of trace salts, at a rate of 1.2 ml/l/h. This last phase can be extended for up to 96 hours. Variations may be introduced by selecting adequate times for adding methanol to the culture, changing methanol concentration and using a double feed of glycerol/methanol, for further improving the production process.

When the methanol initially hits the culture, expression of insulin in some cells begins. The induction of insulin expression occurs before the entire miscible solvent addition step, which can take place for up to 96 hours, is complete. Therefore, Annibali teaches a method including the steps of adding methanol to induce expression and adding methanol to cells already expressing insulin. Instant claim 130 is written in open form. The transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Owing to the open nature of the claim, the method of Annibali anticipates claim 130.

6. With respect to claim 131, the miscible solvent is methanol (col. 25, ln. 20). With respect to claims 135 and 136, Annibali also teaches that the methanol is added with glycerol and trace

salts (col. 25, lines 21 and 25). With respect to claim 137, the pH of the culture medium is maintained between 3.5 to 5.5 (col. 25, ln. 20). With respect to claim 140, the purification steps include cation exchange chromatography (col. 25, lns. 40-50). With respect to claims 141 and 142, the insulin is expressed in *Pichia* (col. 20m lns. 25-50).

7. Thus, in contrast to Applicant's arguments filed 10/16/2008, Annibali teaches each and every limitation of the claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 140 is rejected under 35 U.S.C. 103(a) as being unpatentable over Annibali (US Patent No. 7,091,032), as applied to claims 130, 131, 135-137, 141 and 142 above, in view of Willis (*Modern Drug Discov.*, **2001**, *4*, 43-44).

10. Annibali teaches a process for the recovery of recombinant insulin including treating a culture medium comprising cells for expressing insulin with a water miscible solvent and isolating the insulin from the mixture (col. 25, lines 1-50). With respect to the limitation "treating an expression broth/culture medium containing the expressing cells with a one or more

water miscible organic solvents to give a mixture", Annibali teaches that the purpose of the miscible solvent addition is to induce insulin expression. The process of adding methanol in Annibali occurs over a time period (col. 25, ln. 17-26):

> Once the growing phase of the biomass was completed, the cells were kept without feeding for half an hour and the production phase begun. During said phase pH was regulated from 3.5 to 5.5, and 100% methanol was added plus 12 ml/l of trace salts, at a rate of 1.2 ml/l/h. This last phase can be extended for up to 96 hours. Variations may be introduced by selecting adequate times for adding methanol to the culture, changing methanol concentration and using a double feed of glycerol/methanol, for further improving the production process.

11. When the methanol initially hits the culture, expression of insulin in some cells begins. The induction of insulin expression occurs before the entire miscible solvent addition step, which can take place for up to 96 hours, is complete. Therefore, Annibali teaches a method including the steps of adding methanol to induce expression and adding methanol to cells already expressing insulin. Instant claim 130 is written in open form. The transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Owing to the open nature of the claim, the method of Annibali anticipates claim 130.

12. With respect to claim 131, the miscible solvent is methanol (col. 25, ln. 20). With respect to claims 135 and 136, Annibali also teaches that the methanol is added with glycerol and trace salts (col. 25, lines 21 and 25). With respect to claim 137, the pH of the culture medium is maintained between 3.5 to 5.5 (col. 25, ln. 20). With respect to claim 140, the purification steps include cation exchange chromatography (col. 25, lns. 40-50). With respect to claims 141 and 142, the insulin is expressed in *Pichia* (col. 20m lns. 25-50).

13. With respect to claim 140, Annibali does not teach the use of expanded-bed chromatography.

14. Willis teaches that expanded-bed chromatography is a technique that combines the step of sample preparation with the first stage of chromatography, and is advantageous for use in methods for purification of recombinantly expressed proteins in cells.

15. It would have been obvious to the skilled artisan to substitute expanded-bed chromatography taught by Willis for the traditional chromatography in the method taught by Annibali, satisfying the limitation of claims 140. The skilled artisan would have been motivated to make the substitution based on the teaching of Willis: "The advantage is a higher recovery," says Guenter Jagschies, vice president of industrial separations for Amersham Biosciences. "That's where the money comes out for the customer." Jagschies says that EBA users often see a 25% increase in their recovery. "That is very important," he continues, "because we are talking about the first step in the downstream process, and you can never have more product after any later step. You always lose something." There would have been a reasonable expectation of success given that expanded-bed chromatography supplies are commercially available (Willis). Thus, the invention as a whole was clearly obvious to one of ordinary skill in the art at the time the invention was made.

16. Applicant traversed the rejection in the response filed 10/16/2008, on the grounds that the claimed invention relates to a step which is performed after the proteins are expressed in the cell culture, wherein the expressed protein are extracted and isolated from the culture medium/broth by treating the culture medium/broth with one or more water miscible solvents. This argument is not persuasive. Broadest reasonable interpretation of claim 130 includes additional steps beyond

those explicitly recited owing to the use of the open transitional phrase "comprising." Therefore, Annibali which teaches a method of adding methanol to cells to induce expression of insulin, continuing to add methanol to said culture over a time period pf up to 96 hours and isolating said insulin, reads on the instant method. Furthermore, the claims as written are not limited to a method of extracting and isolating insulin with a water miscible solvent. The only method step that is actively and positively recited in the claim is one of treating an expression broth/culture with a water miscible solvent to give a mixture and isolating the insulin from the mixture. Annibali clearly teaches this method. Annibali teaches adding methanol to the culture which results in the formation of a mixture. In a downstream step, Annibali teaches isolating the insulin. The instant claims are not limited to an embodiment in which the water miscible solvent is used to extract insulin from the broth/culture. Prior art describing the treating of the culture/broth with a water miscible solvent, albeit for a different purpose than extracting, reads on the instant claims.

17. Applicant traverse the rejection in the response filed 10/16/2008 on the grounds that Willis does not correct the deficiencies of Annibali. This is not persuasive. Annibali anticipates claim 130 for the reasons set forth above. The additional limitation of claim 140 only requires that the method of isolation be a expanded-bed cation exchange chromatography step. Annibali teaches the use of cation exchange chromatography in the method of purifying insulin. Annibali doe not teach expanded-bed chromatography. Willis teaches the significant advantages of expanded bed chromatography relative to conventional chromatography. The skilled artisan following the method of Annibali would be motivated to improve the method by using expanded-bed chromatography taught by Willis for the reasons set forth above. It is not

necessary for Willis to teach solvent extraction as a means for purifying insulin in order for the references to be combined. Annibali teaches all other claim limitations. Willis is relied upon merely for the teaching of expanded-bed chromatography.

18. The rejection over Annibali, Willis, Trinh *et al.* and Scopes *et al.* is moot.

19. Claims 132 and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Annibali (US Patent No. 7.091,032) as applied to claims 130, 131, 135-137, 141 and 142, above in further view of Scopes (Protein Purification: Principles and Practice, Springer, New York, 1994, pp 85-93) and Gerlough & Bates (*J. Pharm. Exp. Therapeutics*, **1932**, Vol. XLV, No. 1, pp. 19-51).

20. Annibali does not teach the use of other water miscible organic solvents to the culture medium to purify the recombinant insulin.

21. Gerlough & Bates teach a method of purifying insulin comprising alcohol precipitation of insulin (pages 20 and 21). Specifically, minced beef pancreas were extracted in 60 to 65 per cent alcohol acidulated with HCl; the extract centrifuged off, neutralized to precipitate the bulk of the physiologically inert proteins and then filtered. The clear alcoholic filtrate was acidified to approximately pH 3.3 and concentrated to one-tenth its volume. Then $(NH_4)_2SO_4$ was added to salt out the insulin together with a large quantity of inert proteins. The precipitant was defatted with an alcohol-ether mixture, dried and the dispersed in water. The reaction was maintained between pH 2.5 and 2.8. The crude insulin was again salted out by the addition of Na_2SO_4. The wet precipitate was taken up in water and alcohol. The insoluble precipitate was centrifuged off,

dispersed in water and extracted with 60 per cent alcohol. The precipitate was again centrifuged off and reextracted a third time. All of the extracts were combined, precipitated in 90 to 92 per cent alcohol. The precipitate was washed with ether, dried and then taken up with water and reprecipitated three times isoelectrically at pH 5.0 to remove slats ad inert soluble pancreas protein.

22. Scopes teaches that the method of protein precipitation by water-miscible organic solvents has been employed since the early days of protein purification (page 85). The two most widely used solvents are ethanol and acetone (page 87). Others that can be used include methanol, isopropanol, and dioxin (page 87). The first step can involve the addition of 20-30% solvent, increasing in subsequent steps to 50% (pages 88-89).

23. It would have been obvious to the skilled artisan to add a precipitation step as an additional step to the purification protocol taught by Annibali, according to the teaching of Gerlough & Bates and Scopes. Precipitation is a standard and routine method used for protein purification, as evidenced by Scopes, and a method that has been used successfully for the purification of insulin, as evidenced by Gerlough & Bates. All of the elements of the claimed methods were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods and through routine experimentation, with no change in their respective functions, to yield the predictable result of insulin purification. It is routine in the protein purification art to combine different methods of separation, precipitation, chromatography and dialysis to improve purification protocols. Thus, the invention as a whole was clearly obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

24. No claims are allowed.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

26. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

28. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654